Rominger A, Saam T, Wolpers S *et al.* (2009) 18F-FDG PET/CT identifies patients at risk for future vascular events in an otherwise asymptomatic cohort with neoplastic disease. *J Nucl Med* 50:1611–20

Rosenson RS, Brewer HB Jr., Davidson WS *et al.* (2012) Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. *Circulation* 125:1905–19

Schwartz GG, Olsson AG, Abt M *et al.* (2012) Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 367:2089–99

Taylor AJ, Villines TC, Stanek EJ *et al.* (2009) Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med* 361:2113–22

Vaisman BL, Remaley AT (2013) Measurement of lecithin-cholesterol acyltransferase activity with the use of a Peptide-proteoliposome substrate. *Methods Mol Biol* 1027:343–52

Yeung H, Takeshita J, Mehta NN *et al.* (2013) Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol* 149:1173–9

Yu Y, Sheth N, Krishnamoorthy P *et al.* (2012) Aortic vascular inflammation in psoriasis is associated with HDL particle size and concentration: a pilot study. *Am J Cardiovasc Dis.* 2:285–92

See related article on pg 677

Inflammasome Activation by *Propionibacterium acnes*: The Story of IL-1 in Acne Continues to Unfold

Diane M. Thiboutot[1]

Insights into the immune mechanisms at play in skin diseases including acne continue to be made. In this issue, Kistowska *et al.* confirm that *Propionibacterium* acnes activates inflammasomes leading to the production of IL-1β and they further identify putative mechanisms by which this process occurs. These data raise interesting questions regarding a multipronged approach by which *P. acnes* elicits inflammation in early versus late acne and putative differences in the effects of IL-1α and IL-1β in this disease process.

Journal of Investigative Dermatology (2014) **134,** 595–597. doi:10.1038/jid.2013.528

Propionibacterium acnes is the predominant organism in the microbiome of facial skin (Grice *et al.*, 2009). Although thought to be commensal, *P. acnes* exerts a variety of pro-inflammatory activities most notable in patients with acne vulgaris. This intriguing organism orchestrates a multipronged approach to trigger innate immunity in acne by activating toll-like receptor 2 and, as reported now, inflammasomes (Kim *et al.*, 2002; Kistowska *et al.*, 2014; Qin *et al.*, 2014).

As reported in this issue, remarkable convergence with respect to inflammasome activation by *P. acnes* has been achieved (Kistowska *et al.*, 2014; Qin *et al.*, 2014). Kistowska *et al.* (2014) present a series of elegant experiments that confirm and expand upon the recent seminal findings of Qin *et al.* (2014). Using a combination of *in vitro* and *in vivo* assays, including inflammasome activation in monocytes, immunohistochemistry of inflammatory acne lesions from patients, a mouse ear model for *P. acnes*-induced inflammation, and transgenic mouse models of several defects in the inflammasome pathway, Kistowska *et al.* (2014) confirm that *P. acnes* induces inflammasome activation in human monocytes that is mediated by NLRP3 leading to cleavage of pro-IL-1β to active IL-1β via caspase 1. The authors demonstrate that the release of IL-1β by monocytes in response to *P. acnes* requires phagocytosis, lysosomal damage with release and activation of cathepsin B, generation of reactive oxygen species, and K+ efflux as pointed out in their recent commentary (Contassot and French, 2014). Furthermore, they propose that IL-1β secreted from myeloid cells in a NLRP3-inflammasome-dependent manner, is responsible for the induction of a neutrophilic inflammatory response to *P. acnes in vivo* (Kistowska *et al.*, 2014).

In view of these advances, it becomes even more compelling to examine how and where *P. acnes* interacts with immune cells (including keratinocytes) in the distinct microenvironments of early versus late acne lesions. This question is relevant clinically in that understanding the pro-inflammatory actions of *P. acnes* in very early acne may aid in identifying targets to suppress early inflammation and thus to avoid intensification of the inflammatory response that follows follicular rupture. Kistowska *et al.* (2014) injected *P. acnes* into the dermis of the mouse ear to model late stage acne. In the dermis, *P. acnes* may be phagocytised by myeloid cells, leading to inflammasome activation, secretion of IL-1β and a neutrophilic response (Kistowska *et al.*, 2014). They conclude that myeloid cells are key players in inflammasome activation in acne.

In early acne, however, follicles are surrounded by an infiltrate of lymphocytes and macrophages, and *P. acnes* is contained within the intact follicle in proximity to follicular keratinocytes (Layton *et al.*, 1998; Jeremy *et al.*, 2003). Very little is known about the dynamics of myeloid cell infiltration into follicles at this early stage. Toyoda and Morohashi, (2001) published electron micrographs depicting macrophages in close proximity to follicular keratinocytes, but whether these were early or late lesions and whether the follicles were intact or disrupted were not specified. Neutrophils were noted to infiltrate the follicles and reach the cornified layers, but it is uncertain whether these neutrophils interacted with *P. acnes* contained within the follicles (Toyoda and Morohashi, 2001).

[1]*Department of Dermatology, Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA*

Correspondence: Diane M. Thiboutot, Pennsylvania State University College of Medicine, Department of Dermatology, UPC 2 Room 4300 P.O. Box 850, Hershey 17033, Pennsylvania, USA.
E-mail: dthiboutot@psu.edu

Clinical Implications

- Remarkable convergence appears to have been achieved regarding inflammasome activation by *Propionibacterium acnes*.
- The work reported by Kistowska *et al.* confirms and extends the conclusion that *P. acnes* activates inflammasomes, leading to IL-1β release, most likely within the dermis.
- This work offers prospects for novel therapies to be directed against inflammatory acne.

Interaction of *P. acnes* with follicular keratinocytes may be important in early acne. Fifteen years ago, Guy and Kealey, (1998a, b) demonstrated that IL-1α leads to hyperkeratinization of infundibular segments of follicles in a fashion that is similar to what is seen in the microcomedones of early acne. Also, material extracted from comedones from acne patients demonstrated high levels of IL-1α-like activity (Ingham *et al.*, 1992). Selway (2013) recently used the organ culture model of Guy and Kealey, (1998a, b) to demonstrate that follicular keratinocytes secrete IL-1α in response to peptidoglycan, a component of the cell wall of *P. acnes* that activates TLR2. These authors suggest that TLR activation and secretion of IL-1α from keratinocytes may be initiating steps in comedogenesis and, therefore, critical to the pathogenesis. Although not examined in this study, it would be very interesting to determine whether *P. acnes* itself activates TLR2 on follicular keratinocytes in this model.

Although studies demonstrate that stimulation of keratinocytes by *P. acnes* leads to secretion of IL-1α, there is discordance in the literature concerning this finding (Walters *et al.*, 1995; Ingham *et al.*, 1998; Graham *et al.*, 2004; Nagy *et al.*, 2005; Akaza *et al.*, 2009; Lee *et al.*, 2010; Selway, 2013). A summary of the published studies is presented in Table 1. Akaza *et al.* (2009) and Graham *et al.* (2004) report that keratinocytes secrete IL-1α when exposed to live or heat-killed *P. acnes* in the stationary growth phase, but studies by Ingham *et al.* (1998) and Walters *et al.* (1995) do not. Of note is that differences in *P. acnes* strains, growth phases of the bacteria, use of viable or killed *P. acnes*, differing methods used to kill *P. acnes*, and differences in use of *P. acnes* whole cells, cellular components, or culture supernatants may account for the variations reported for IL-1α secretion following *P. acnes* exposure. Close examination of the experimental details of earlier studies reveals several plausible explanations for the differing results. We now know that *P. acnes* activates TLR2 on keratinocytes leading to cytokine production, and that the *P. acnes* proteins responsible for TLR activation are associated with the cell wall. In the studies by Walters *et al.* (1995) and Ingham *et al.* (1998), the cell wall fraction of *P. acnes* was discarded, and the keratinocytes were exposed to intracellular fractions of *P. acnes*, which would decrease the likelihood of TLR2 activation. Also in these studies and in one experiment reported by Graham *et al.* (2004), *P. acnes* was inactivated using formaldehyde, which again may alter the surface proteins of *P. acnes* and blunt the ability of the organism to activate TLR2 on keratinocytes.

Kistowska *et al.* (2014) demonstrate that keratinocytes are unable to secrete mature IL-1β following exposure to one strain of heat-killed *P. acnes*. Additional experimental details, such as the growth phase of the organism, would be helpful in interpreting this finding. It would also be important to conduct these experiments using additional strains of *P. acnes* before drawing the general conclusion that *P. acnes* is unable to stimulate IL-1β secretion in keratinocytes.

Table 1. Effect of *P. acnes* on keratinocyte expression or secretion of IL-1α

Study	*P. acnes* strain(s)	Growth phase	*P. acnes* component	Viability	IL-1α
Ingham *et al.*, 1998	Clinical isolate	48-h Stationary	Intracellular soluble cell fraction	Sheared cells (cell wall fraction removed)	ELISA (−)
Walters *et al.*, 1995	Clinical isolate	48-h Stationary	Whole cell	Formaldehyde-killed	ELISA (−)
			Culture supernatant		ELISA (−)
			Intracellular soluble cell fraction	Sheared cells (cell wall fraction removed)	ELISA (−)
Graham *et al.*, 2004	P37	24-h Exponential	Whole cell	Live	ELISA (−)
				Formaldehyde-killed	ELISA (−)
Graham *et al.*, 2004	P37	48-h Stationary	Whole cell	Live	ELISA (+)
				Formaldehyde-killed	ELISA (−)
Nagy *et al.*, 2005	889,2005,6609 ATCC 11828	48-h Stationary	Whole cell	Live	mRNA (−)
Akaza *et al.*, 2009	JCM 6425	48-h Stationary	Whole cell	Live	ELISA (+)
	JCM 6473 5 clinical isolates			Heat-killed	All strains and all viabilities
Lee *et al.*, 2010	ATCC 6919	24-h Exponential	Culture supernatant		mRNA (+)

Despite the fact that acne may be the most common skin disease, it is clear that there are missing pieces in its puzzling pathogenesis. This excellent work by Kistowska *et al.* (2014) validates the recent work of Qin *et al.* (2014) and takes the field one step closer to understanding the immunologic mechanisms at play in acne. Important next steps would be to examine the mechanisms by which *P. acnes* activates the innate immune response within the unique microenvironments that arise during acne lesion development and to examine the respective roles of IL-1α and IL-1β in this process.

CONFLICT OF INTEREST
The author states no conflict of interest.

REFERENCES

Akaza N, Akamatsu H, Kishi M *et al.* (2009) Effects of *Propionibacterium acnes* on various mRNA expression levels in normal human epidermal keratinocytes *in vitro*. *J Dermatol* 36:213–23

Contassot E, French LE (2014) New insights into inflammatory acne pathogenesis: *Propionibacterium acnes* activates the inflammasome. *J Invest Dermatol,* doi:10.1038/JID.2013.505

Graham GM, Farrar MD, Cruse-Sawyer JE *et al.* (2004) Proinflammatory cytokine production by human keratinocytes stimulated with *Propionibacterium acnes* and *P. acnes* GroEL. *Br J Dermatol* 150:421–8

Grice EA, Kong HH, Conlan S *et al.* (2009) Topographical and temporal diversity of the human skin microbiome. *Science* 324:1190–2

Guy R, Kealey T (1998a) The effects of inflammatory cytokines on the isolated human sebaceous infundibulum. *J Invest Dermatol* 110: 410–5

Guy R, Kealey T (1998b) Modelling the infundibulum in acne. *Dermatology* 196:32–7

Ingham E, Eady EA, Goodwin CE *et al.* (1992) Pro-inflammatory levels of interleukin-1 alpha-like bioactivity are present in the majority of open comedones in acne vulgaris. *J Invest Dermatol* 98:895–901

Ingham E, Walters CE, Eady EA *et al.* (1998) Inflammation in acne vulgaris: failure of skin micro-organisms to modulate keratinocyte interleukin 1 alpha production *in vitro*. *Dermatology* 196:86–8

Jeremy AHT, Holland DB, Roberts SG *et al.* (2003) Inflammatory events are involved in acne lesion initiation. *J Invest Dermatol* 121:20–7

Kim J, Ochoa M-T, Krutzik SR *et al.* (2002) Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. *J Immunol* 169:1535–41

Kistowska M, Gehrke S, Jankovic D *et al.* (2014) IL-1β drives inflammatory responses to *Propionibacterium acnes in vitro* and *in vivo*. *J Invest Dermatol* 134:677–85

Layton AM, Morris C, Cunliffe WJ *et al.* (1998) Immunohistochemical investigation of evolving inflammation in lesions of acne vulgaris. *Exp Dermatol* 7:191–7

Lee S, Kim J-M, Jeong S *et al.* (2010) Protease-activated receptor-2 mediates the expression of inflammatory cytokines, antimicrobial peptides, and matrix metalloproteinases in keratinocytes in response to *Propionibacterium acnes*. *Arch Dermatol Res* 302:745–56

Nagy I, Pivarcsi A, Koreck A *et al.* (2005) Distinct strains of *Propionibacterium acnes* induce selective human β-defensin-2 and interleukin-8 expression in human keratinocytes through toll-like receptors. *J Invest Dermatol* 124:931–8

Qin M, Pirouz A, Kim M-H *et al.* (2014) *Propionibacterium acnes* induces IL-1β secretion via the NLRP3 inflammasome in human monocytes. *J Invest Dermatol* 134:381–8

Selway JL (2013) Toll-Like receptor 2 activation and comedogenesis: implications for the pathogenesis of acne. *BMC Dermatol* 13:10

Toyoda M, Morohashi M (2001) Pathogenesis of acne. *Med Electron Microsc* 34:29–40

Walters CE, Ingham E, Eady EA *et al.* (1995) *In vitro* modulation of keratinocyte-derived interleukin-1 alpha (IL-1 alpha) and peripheral blood mononuclear cell-derived IL-1 beta release in response to cutaneous commensal microorganisms. *Infect Immun* 63:1223–8

See related article on pg 712

The Adverse Effect of IFN Gamma on Stratum Corneum Structure and Function in Psoriasis and Atopic Dermatitis

Kenneth R. Feingold[1]

There is a marked increase in cytokines, including interferon gamma, in cutaneous diseases such as atopic dermatitis and psoriasis. In this issue of the Journal, Tawada and colleagues demonstrate that the quantity of ultra long–chain ceramides in the stratum corneum, which play a key role in maintaining the permeability barrier, is reduced in atopic dermatitis and psoriasis. Further, they demonstrate that interferon gamma decreases the expression of the enzymes required for the synthesis of these ultra long–chain ceramides (ELOVLs and ceramide synthase 3). These results suggest that an increase in interferon gamma by decreasing the key enzymes required for the synthesis of ultra long–chain ceramides could further impair permeability barrier function, thereby exacerbating the pathological changes.

Journal of Investigative Dermatology (2014) **134,** 597–600. doi:10.1038/jid.2013.440

It has long been recognized that cytokines, such as tumor necrosis factor (TNF), IL-1, IL-6, and the IFNs, regulate lipid metabolism (Hardardottir *et al.*, 1994; Khovidhunkit *et al.*, 2004). Studies in the 1980s demonstrated that TNF and other cytokines would inhibit fat accumulation in adipocytes by decreasing the activity of lipoprotein lipase and by inhibiting fatty acid synthesis. In contrast, in the liver, TNF and other cytokines stimulate lipid synthesis and VLDL production, which contributes to the elevation in serum triglyceride levels that characteristically occurs during infections and inflammatory diseases. Over the ensuing years, cytokines have been shown to affect a large number of different lipid metabolic pathways in a wide variety of tissues (Hardardottir *et al.*, 1994; Khovidhunkit *et al.*, 2004). Not surpri-

[1]*Metabolism Section, Department of Veterans Affairs Medical Center, University of California, San Francisco, San Francisco, California, USA*

Correspondence: Kenneth R. Feingold, Metabolism Section (111F), Veterans Affairs Medical Center, 4150 Clement Street, San Francisco, California 94121, USA. E-mail: kenneth.feingold@ucsf.edu